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Title of Invention _____

Inventors (please provide full names): _____

_____

Earliest Priority Date: _____

Keywords (include any known synonyms registry numbers, explanation of initialisms):

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___ Other

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___ In-house sequence systems (list)
___ Dialog
___ Dr. Link
___ Westlaw
___ Other (specify)

PTO-1590 (2-99)

7/14/99

67057 Everett White

1623 CM1/ 7A17

09/101,672

Preparation containing a Combination of 5-Methylisoxazole-4-Carboxylic acid-(4-Trifluoromethyl-Anilideand N-(4-Trifluoromethylphenyl) 2-Cyano-3-Hydroxycrotonic acid amide

Robert Bartlett and Johann Then

3/20/96

A copy of the broadest claims (claims 12, 20, 26 and 27) and the Abstract is disclosed.

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=> fil reg
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DICTIONARY FILE UPDATES:  24 JUL  99  HIGHEST RN 228878-07-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

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L28                 STR
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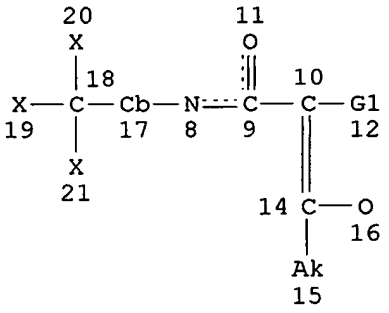


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
L30           45 SEA FILE=REGISTRY CSS FUL L28

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SEARCH TIME: 00.00.01


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                 SAV L30 WHITE101/A
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L38           0 S L14 AND L32

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L40           9 S L39 AND COMBIN?
L41           7 S L39 AND FORMUL?
L42           1 S L39 AND SYNERG?
L43           6 S L39 AND COMPOSITION
L44          18 S L40-L43
L45          19 S L24,L44
                SEL HIT RN

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L46           5 S E6-E11

     FILE 'REGISTRY' ENTERED AT 11:33:59 ON 25 JUL 1999

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=> d 146 ide can tot

L46  ANSWER 1 OF 5  REGISTRY  COPYRIGHT 1999 ACS
RN   214782-56-6  REGISTRY
CN   2-Butenamide, 2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-, (2E)-
     (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C12 H9 F3 N2 O2
SR   CA
LC   STN Files:   CA, CAPLUS, TOXLIT

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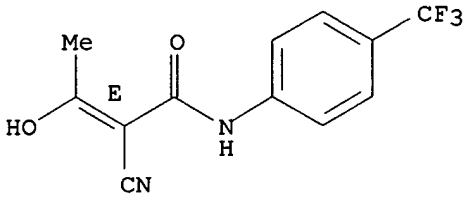


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              1 REFERENCES IN FILE CA (1967 TO DATE)
              1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  129:310393

L46  ANSWER 2 OF 5  REGISTRY  COPYRIGHT 1999 ACS
RN   208401-20-1  REGISTRY
CN   4-Isoxazolecarboxamide, 3-methyl-N-[4-(trifluoromethyl)phenyl]- (9CI)  (CA
     INDEX NAME)
FS   3D CONCORD
MF   C12 H9 F3 N2 O2
SR   CAS Registry Services
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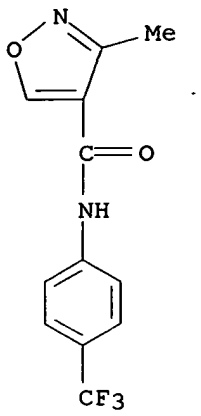

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:20604

L46 ANSWER 3 OF 5 REGISTRY COPYRIGHT 1999 ACS
RN **196191-66-9** REGISTRY
CN 4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]-, mixt. with 2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Butenamide, 2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-, mixt. contg. (9CI)
MF C12 H9 F3 N2 O2 . C12 H9 F3 N2 O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

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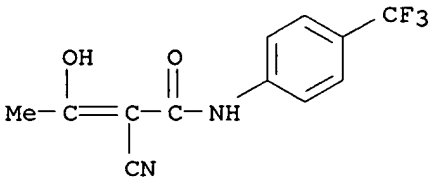
CRN 108605-62-5
CMF C12 H9 F3 N2 O2



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CRN 75706-12-6
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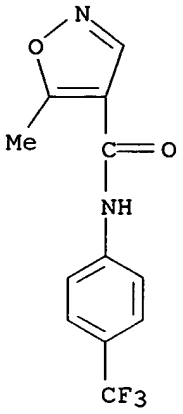
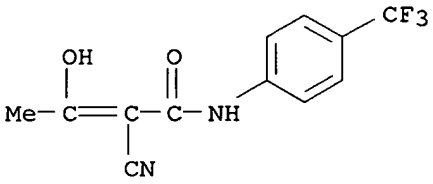


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:268061

L46 ANSWER 4 OF 5 REGISTRY COPYRIGHT 1999 ACS
RN **108605-62-5** REGISTRY
CN 2-Butenamide, 2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Cyano-3-hydroxy-N-(4-trifluoromethylphenyl)crotonamide
CN A 77-1726
CN SU 20
CN Teriflunomide
FS 3D CONCORD
DR **210165-52-9**
MF C12 H9 F3 N2 O2
CI COM
SR CA
LC STN Files: BIOSIS, CA, CANCERLIT, CAPLUS, EMBASE, MEDLINE, TOXLIT, USPATFULL



79 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
79 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:39350

REFERENCE 2: 131:29577

REFERENCE 3: 131:27612

REFERENCE 4: 131:27611

REFERENCE 5: 131:27610

REFERENCE 6: 131:27609

REFERENCE 7: 131:27608

REFERENCE 8: 131:13589

REFERENCE 9: 130:280811

REFERENCE 10: 130:246540

L46 ANSWER 5 OF 5 REGISTRY COPYRIGHT 1999 ACS
RN **75706-12-6** REGISTRY
CN 4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN HWA 486
CN Leflunomide
CN SU 101
CN SU 101 (pharmaceutical)
FS 3D CONCORD
DR 210165-51-8
MF C12 H9 F3 N2 O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
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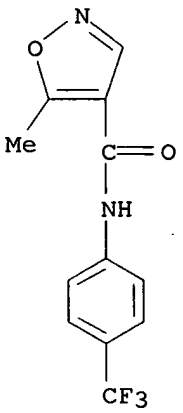

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5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
229 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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REFERENCE 2: 131:27618

REFERENCE 3: 131:27612

REFERENCE 4: 131:27611

REFERENCE 5: 131:13589

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REFERENCE 8: 130:346723

REFERENCE 9: 130:306209

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=> d bib abs hitrn tot l45

L45 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1999:170424 HCAPLUS
DN 131:13589
TI Potentiation of immunosuppressive efficacy by **combining** the novel leflunomide analog, HMR 279, with microemulsion cyclosporine in a rat lung transplant model
AU Hausen, Bernard; Boeke, Katrin; Berry, Gerald J.; Gummert, Jan F.; Christians, Uwe; Morris, Randall E.
CS Transplantation Immunology, Department of Cardiothoracic Surgery, and Department of Pathology, Stanford University, Palo Alto, CA, 94305-5407, USA
SO Transplantation (1999), 67(3), 354-359
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins

DT Journal
LA English
AB Background-The novel leflunomide (LFM) analog, HMR 279, potentiates the immunosuppressive efficacy of microemulsion cyclosporine (Neoral) in rodent heart transplantation. The present study was designed to evaluate the immunosuppressive efficacy of this **combination** in comparison to the **combination** of Neoral and LFM in a stringent allogeneic rodent lung transplant model. Methods-Donor lungs from Brown Norway rats were implanted into Lewis recipients and were followed for 21 days. Postoperative monitoring included daily wt. assessment, chest radiographs, drug trough levels measured by HPLC (LFM/HMR 279) and HPLC/mass spectrometry (Neoral), and blinded histol. assessment of the transplanted lung on the day of death based on the International Society for Heart and Lung Transplantation working **formulation**. Untreated lung recipients served as controls (group I). Rats were assigned to the following treatment groups: II, 7.5 mg/kg/day Neoral; III, 10 mg/kg/day LFM; IV, 10 mg/kg/day HMR 279; V, 10 mg/kg/day LFM plus 7.5 mg/kg/day Neoral given simultaneously; and VI, 10 mg/kg/day HMR 279 plus 7.5 mg/kg/day Neoral given simultaneously. Drugs were given daily by oral gavage. Results-All rats except for one in the HMR 279 monotherapy group survived the follow-up period. The chest radiographs in the control, LFM, and HMR 279 monotherapy groups showed moderate to complete opacification of the left chest by postoperative day 7 (controls) and day 14 (LFM, 279). At postoperative day 21, the Neoral monotherapy and the **combination** groups showed no signs of opacification in the radiographs. **Combination** therapies of Neoral plus HMR 279 or Neoral plus LFM were most successful in preventing histol. allograft rejection. **Combining** Neoral and HMR 279 resulted in a significant decrease in the cyclosporine trough levels. Co-administration of LFM plus Neoral resulted in significantly higher LFM trough levels when compared to LFM monotherapy. Of all treatments studied, the **combination** of HMR 279 plus Neoral was tolerated best as assessed by percentage of wt. change. Conclusion-This study showed for the first time in a stringent rodent lung transplant model that **combined** treatment of LFM or HMR 279 plus Neoral potentiates the immunosuppressive efficacies of these drugs and successfully prevents allograft rejection.
IT **75706-12-6**, Leflunomide
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(comparison with; potentiation of immunosuppressive efficacy by **combining** novel leflunomide analog HMR 279 with microemulsion cyclosporine in rat lung transplant model)
IT **108605-62-5**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(potentiation of immunosuppressive efficacy by **combining** novel leflunomide analog HMR 279 with microemulsion cyclosporine in rat lung transplant model)

L45 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:789148 HCAPLUS
DN 130:20604
TI Heteroarylcarboxamide compounds active against protein tyrosine kinase-related disorders, and preparation thereof
IN McMahon, Gerald; Tang, Peng Cho; Shawver, Laura Kay; Hirth, Klaus Peter
PA Sugen, Inc., USA
SO PCT Int. Appl., 149 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9852944	A1	19981126	WO 1998-US10174	19980518
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 11116479	A2	19990427	JP 1998-10368	19980122
AU 9876879	A1	19981211	AU 1998-76879	19980518

PRAI US 1997-46945 19970519
US 1997-47084 19970519
US 1997-56623 19970820
US 1997-61590 19971010
WO 1998-US10174 19980518

OS MARPAT 130:20604

AB Heteroarylcarboxamides are provided which modulate the activity of protein tyrosine kinases and are expected to be useful in the treatment of abnormal protein tyrosine kinase activity-driven disorders. Also provided are methods for the treatment of inappropriate FGFR activity related disorders with the heteroarylcarboxamide, N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide, as well as the treatment of solid tumor cancers, esp. glioblastoma and astrocytoma, with a **combination** of a nitrosourea, preferably BCNU (carmustin), and N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide.

IT **75706-12-6**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heteroarylcarboxamides active against protein tyrosine kinase-related disorders, and prepn. thereof)

IT **208401-20-1P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heteroarylcarboxamides active against protein tyrosine kinase-related disorders, prepn. thereof, and use with nitrosoureas)

IT **108605-62-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heteroarylcarboxamides active against protein tyrosine kinase-related disorders, prepn. thereof, and use with nitrosoureas)

L45 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:648906 HCAPLUS
DN 130:20319
TI Structural and functional comparison of agents interfering with dihydroorotate, succinate and NADH oxidation of rat liver mitochondria
AU Jockel, Johannes; Wendt, Bernd; Loffler, Monika
CS Institute for Physiological Chemistry, School of Medicine, Philipps-University, Marburg, D-35033, Germany
SO Biochem. Pharmacol. (1998), 56(8), 1053-1060
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal

LA English
AB Mitochondrially bound dihydroorotate dehydrogenase (EC 1.3.99.11) catalyzes the fourth sequential step in the de novo synthesis of uridine monophosphate; this enzyme uses ubiquinone as the proximal and cytochrome oxidase as is the ultimate electron transfer system. Here, seven compds. with proven antiproliferative activity and in vitro antipyrimidine effects were investigated with isolated functional mitochondria of rat tissues in order to differentiate their anti-dihydroorotate dehydrogenase potency vs. putative effects on the respiratory chain enzymes. Ten .mu.M of brequinar sodium, the leflunomide derivs. A77-1726, [2-cyano-3-cyclopropyl-3-hydroxy-enoic acid (4-trifluoromethyl)-amide], MNA 279, (2-cyano-N-(4-cyanophenyl-3-cyclopropyl-3-oxo-propanamide), MNA715 (2-cyano-3-hydroxy-N-4-(trifluoromethyl)-phenyl-6-heptanamide), HR325 (2-cyano-3-cyclopropyl-3-hydroxy-N-[3'-methyl-4'-(trifluoromethyl)phenyl]-propenamide), and the diazine toltrazuril completely inhibited the dihydroorotate-induced oxygen consumption of liver mitochondria. Succinate and NADH oxidn. were found to be influenced only at elevated drug concn. (100 .mu.M), with the exception of HR325, 10 .mu.M of which caused a 70% inhibition of NADH and 50% inhibition of succinate oxidn. This was comparable to the effects of toltrazuril, which caused an approx. 75% inhibition of NADH oxidn. Ciprofloxacin was shown here to have only marginal effects on the redox activities of the inner mitochondrial membrane. This differentiation of drug effects on mitochondrial functions will contribute to a better understanding of the in vivo pharmacol. activity of these drugs, which are presently in clin. trials because of their immunosuppressive, cytostatic or anti-parasitic activity. A comparison of the influence of A77-1726, HR325, brequinar and 2,4-dinitrophenol on energetically coupled rat liver mitochondria revealed only a weak uncoupling potential of A77-1726 and brequinar. In addn., a modeling study was raised to search for common spatial arrangements of functional groups essential for binding of inhibitors to dihydroorotate dehydrogenase. From the structural comparison of different metabolites and inhibitors of pyrimidine metab., a 6-point model was obtained by conformational anal. for the drugs tested on mitochondrial functions, pharmacophoric perception and mapping. We propose our model in **combination** with kinetic data for a rational design of highly specific inhibitors of dihydroorotate dehydrogenase. ← NA
IT **75706-12-6**, Leflunomide **108605-62-5**, A77-1726
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural and functional comparison of agents interfering with dihydroorotate, succinate and NADH oxidn. of rat liver mitochondria)

L45 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:606894 HCAPLUS
DN 129:310393
TI Isoxazolylthioamides as potential immunosuppressants. A **combinatorial** chemistry approach
AU Albert, Rainer; Knecht, Hellmut; Andersen, Elsebeth; Hungerford, Valerie; Schreier, Max H.; Papageorgiou, Christos
CS Novartis Pharma AG, Transplantation Research, BASEL, CH-4002, Switz.
SO Bioorg. Med. Chem. Lett. (1998), 8(16), 2203-2208
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 129:310393
AB A library of thioamide derivs. of leflunomide and of its bioactive metabolite has been synthesized on solid phase. Thus, para-substituted

phenylacetic acids were coupled to TentaGel and were subsequently reacted with arom. isothiocyanates. Treatment of the resulting enaminothioamides with hydroxylamine led to their simultaneous cyclization and cleavage from the resin affording 23 derivs. Their in vitro profiling demonstrated that the amide-thioamide isologous substitution was detrimental of the biol. activity.

IT **75706-12-6**, Leflunomide **214782-56-6**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isoxazolylthioamides as potential immunosuppressants using **combinatorial** chem. approach in relation to structure)

L45 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:542534 HCAPLUS
DN 129:254610
TI Inhibition of anti-CD3 antibody-induced mouse T cell activation by pentoxifylline in **combination** with rapamycin or A77 1726 (leflunomide)
AU Richard, Martin; Hoskin, David W.
CS Department of Microbiology and Immunology, Faculty of Medicine, Dalhousie University, Halifax, NS, B3H 4H7, Can.
SO Int. J. Immunopharmacol. (1998), 20(4/5), 241-252
CODEN: IJIMDS; ISSN: 0192-0561
PB Elsevier Science Ltd.
DT Journal
LA English
AB Pentoxifylline (PTX), rapamycin (RAP), and leflunomide and potent immunomodulatory drugs with differing modes of action. To develop new drug **combinations** for immunotherapy, we tested the effects of PTX in **combination** with RAP or A77 1726 (the active metabolite of leflunomide) on in vitro T cell activation in a mouse model system. T lymphocytes in spleen cell prepns. were stimulated with anti-CD3 monoclonal antibody alone, or in the presence of PTX (25-200 .mu.g/mL), RAP (0.5-5.0 ng/mL), A77 1726 (2.5-10.0 .mu.M), PTX/RAP (25-200 .mu.g/mL and 0.5-5.0 ng/mL, resp.), or PTX/A77 1726 (25-200 .mu.g/mL and 2.5-10.0 .mu.M, resp.). Anti-CD3-induced T cell proliferation was inhibited in a dose-dependent fashion by the individual drugs. An additive inhibitory effect was obsd. in cultures treated with PTX/RAP or PTX/A77 1726. The effects of PTX, RAP, A77 1726, PTX/RAP, or PTX/A77 1726 (at concns. approximating the IC50 of individual drugs for inhibition of lymphoproliferation) on anti-CD3-activated killer (AK) cell induction, CD25 expression, and interleukin-2 (IL-2) synthesis in anti-CD3-activated spleen cell cultures were also detd. Alone, each drug was able to suppress AK cell induction to varying degrees. PTX plus RAP exhibited strong **synergism**, while the **combination** of PTX and A77 1726 had an additive inhibitory effect on AK cell induction. CD25 expression was only weakly inhibited by A77 1726, but the percentage of CD25-expressing cells was greatly reduced in cultures treated with PTX or RAP. The **combination** of PTX and RAP had an additive inhibitory effect on CD25 expression while PTX and A77 1726 together had an effect equiv. to PTX alone. IL-2 synthesis was inhibited by PTX but was unaffected by RAP or A77 1726. Treatment with PTX plus RAP led to a further redn. in IL-2 prodn. but co-treatment with PTX and A77 1726 approximated the inhibitory effect of PTX alone. We conclude that the **combination** of PTX and RAP is noteworthy for its potent immunomodulatory activity and may be of use in clin. situations where it is desirable to prevent T cell activation.

IT **108605-62-5**, A 77 1726
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(A 77 1726; inhibition of anti-CD3 antibody-induced mouse T cell activation by pentoxifylline in **combination** with rapamycin or A77 1726 (leflunomide))

IT **75706-12-6**, Leflunomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of anti-CD3 antibody-induced mouse T cell activation by pentoxifylline in **combination** with rapamycin or A77 1726 (leflunomide))

L45 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:484936 HCAPLUS
DN 129:127164
TI **Formulation** and method for treating neoplasms by inhalation
IN Placke, Michael E.; Omondi, Anthony R.; Booker, Michael J.; Frye, John E.; Shah, Praful K.; Flanagan, Douglas R., Jr.; Donovan, Maureen D.
PA Battelle Memorial Institute, USA
SO PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9829110	A2	19980709	WO 1997-US24289	19971230
WO 9829110	A3	19990415		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9870975	A1	19980731	AU 1998-70975	19971230
PRAI US 1996-33789	19961230			
WO 1997-US24289	19971230			

AB A **formulation**, method, and app. for treating neoplasms such as cancer by administering a pharmaceutically effective amt. of highly toxic **compn.** by inhalation, wherein the **compn.** is a non-encapsulated antineoplastic drug.
IT **75706-12-6**, SU 101 **210165-52-9**, SU 20 (pharmaceutical)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**formulation** and method for treating neoplasms by inhalation)

L45 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:410142 HCAPLUS
DN 129:183669
TI Leflunomide and the malononitriloamides in xenotransplantation
AU Bartlett, R. R.; Kemp, E.
CS Immunopharmacology Laboratory, Wiesbaden, Germany
SO Xenotransplantation (2nd Ed.) (1997), 641-648. Editor(s): Cooper, David K. C. Publisher: Springer, Berlin, Germany.
CODEN: 66HVAC
DT Conference; General Review
LA English

AB A review with 36 refs. on the use of leflunomide and the malononitriloamides (derivs. of A771726) in preventing acute and chronic allograft as well as xenograft rejection. Since leflunomide and malononitriloamides are rather unique for use with xenotransplantation and considering the advantage of the shorter half-lives of the malononitriloamides, these drugs used in **combination** with other immunosuppressants may be useful to prevent or reverse the rejection of xenografts in humans.

IT **75706-12-6**, Leflunomide **108605-62-5D**, A771726, derivs.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leflunomide and malononitriloamides as immunosuppressants in xenotransplantation to prevent or reverse rejection)

L45 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:154466 HCAPLUS
DN 128:265737
TI Dihydroorotate dehydrogenase inhibitors: quantitative structure-activity relationship analysis
AU Ren, Shijun; Wu, Sharon K.; Lien, Eric J.
CS School of Pharm., Univ. Southern California, Los Angales, CA, USA
SO Pharm. Res. (1998), 15(2), 286-295
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum Publishing Corp.
DT Journal
LA English
AB The main purpose of this study is to analyze the QSAR of 2 series of dihydroorotate dehydrogenase inhibitors (leflunomide and quinolinecarboxylic acid analogs), and to det. the structural requirements for optimum activity of these analogs. A new CQSAR program was used in deriving regression equations and calcg. the octanol/water partition coeff. and the molar refractivity values. The mol. modeling was performed by using the HyperChem program. Statistically significant correlations were obtained using a **combination** of 3-4 parameters. The structural requirements for optimum activity and crit. regions for the inhibitory activity of dihydroorotate dehydrogenase were identified. The QSAR anal. demonstrated that 2 series of dihydroorotate dehydrogenase inhibitors may bind to different binding sites on the enzyme. These results provide a better understanding of dihydroorotate dehydrogenase inhibitor-enzyme interactions, and may be useful for further modification and improvement of inhibitors of this important enzyme.

← NA

IT **108605-62-5**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(QSAR anal. of dihydroorotate dehydrogenase inhibitors)

IT **75706-12-6D**, Leflunomide, metabolites, analogs
108605-62-5D, analogs
RL: PRP (Properties)
(QSAR anal. of dihydroorotate dehydrogenase inhibitors)

L45 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:655394 HCAPLUS
DN 127:311457
TI Solid pharmaceutical **composition** comprising leflunomide
IN Siefke, Verena; Mentrup, Edgar
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DT Patent

LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 797989	A1	19971001	EP 1997-104344	19970314
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	DE 19612131	A1	19980122	DE 1996-19612131	19960327
	AU 9716513	A1	19971002	AU 1997-16513	19970325
	CA 2201040	AA	19970927	CA 1997-2201040	19970326
	JP 10007547	A2	19980113	JP 1997-72937	19970326
PRAI	DE 1996-19612131	19960327			

AB Leflunomide tablets are manufd. under essentially anhyd. conditions to minimize decompn. to N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (I) during storage. Thus, a mixt. of leflunomide 10.0, lactose 78.0, corn starch 50.0, highly disperse SiO2 0.5, crosslinked PVP 7.5, and Mg stearate was subjected to direct tableting without wet granulation. After 6 mo storage at 40.degree. and relative humidity 75%, the tablets had a I (impurity) content of only 1.5%.

IT **75706-12-6**, Leflunomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid pharmaceutical **compn.** comprising leflunomide)

IT **108605-62-5P**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(solid pharmaceutical **compn.** comprising leflunomide)

L45 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:640582 HCAPLUS
DN 127:268062
TI Topical **formulations** for treatment of nail psoriasis
IN Petri, Walter
PA Hoechst A.-G., Germany; Petri, Walter
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9734644	A1	19970925	WO 1997-EP905	19970226
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2248977	AA	19970925	CA 1997-2248977	19970226
	AU 9718767	A1	19971010	AU 1997-18767	19970226
	EP 888138	A1	19990107	EP 1997-905085	19970226
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI				
PRAI	DE 1996-19610482	19960316			
	WO 1997-EP905	19970226			

AB Topical **formulations** suitable for treatment of nail psoriasis contain an active agent against psoriasis, .gtoreq.1 spreading solvent, .gtoreq.1 readily volatile solvent, a film-forming agent, and optionally a permeation enhancer. The film-forming agent prevents removal of the active agent during bathing. Thus, a topical prepn. contained leflunomide 0.1, iso-Pr palmitate 2.0, iso-PrOH 33.0, EtOAc 33.0, and Gantrez ES435 31.9 g.

IT **75706-12-6**, Leflunomide **108605-62-5**,
2-Cyano-3-hydroxy-N-(4-trifluoromethylphenyl)crotonamide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical **formulations** for treatment of nail psoriasis)

L45 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:640540 HCAPLUS
DN 127:268061
TI Preparation containing a combination of 5-methylisoxazole-4-carboxylic acid 4-trifluoromethylanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide
IN Bartlett, Robert; Then, Johann
PA Hoechst A.-G., Germany; Bartlett, Robert; Then, Johann
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9734600	A1	19970925	WO 1997-EP1167	19970307
	W: AU, BG, BR, BY, CA, CN, CZ, HU, JP, KR, MX, NO, NZ, PL, RO, RU, SG, SI, TR, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19610955	A1	19970925	DE 1996-19610955	19960320
	CA 2249348	AA	19970925	CA 1997-2249348	19970307
	AU 9719261	A1	19971010	AU 1997-19261	19970307
	AU 705692	B2	19990527		
	EP 896537	A1	19990217	EP 1997-907081	19970307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
	CN 1213302	A	19990407	CN 1997-193041	19970307
	NO 9804343	A	19980918	NO 1998-4343	19980918
PRAI	DE 1996-19610955	19960320			
	WO 1997-EP1167	19970307			

AB A solid prepn. contg. 5-methylisoxazole-4-carboxylic acid 4-trifluoromethylanilide (I) and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (II) shows synergistic activity as an immunosuppressant. Thus, a combination of I (9.7 mg/kg) and II (0.3 mg/kg), administered orally to rats once a day for 12 days as a suspension in 1% aq. CM-cellulose, was effective against adjuvant-induced arthritis.
IT **196191-66-9**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical combination of methylisoxazolecarboxylic acid trifluoromethylanilide and (trifluoromethylphenyl)cyanohydroxycrotonamide)

L45 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:204396 HCAPLUS
DN 126:268519
TI Pharmaceutical **formulations** for lipophilic compounds comprising. ethanol and a surfactant
IN Schwartz, Donna P.; Shawver, Laura K.
PA Sugen, Inc., USA
SO U.S., 7 pp. Cont.-in-part of U.S. Ser.No. 370,574.
CODEN: USXXAM
DT Patent

LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5610173	A	19970311	US 1995-429206	19950426
	US 5700823	A	19971223	US 1994-179570	19940107
	US 5700822	A	19971223	US 1995-457047	19950601
	WO 9633745	A1	19961031	WO 1996-US5500	19960417
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2215327	AA	19961031	CA 1996-2215327	19960417
	AU 9655604	A1	19961118	AU 1996-55604	19960417
	AU 700423	B2	19990107		
	EP 830145	A1	19980325	EP 1996-912954	19960417
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1182371	A	19980520	CN 1996-193486	19960417
	JP 10511683	T2	19981110	JP 1996-532614	19960417
	US 5783592	A	19980721	US 1997-813377	19970306
	NO 9704868	A	19971022	NO 1997-4868	19971022
PRAI	US 1994-179570	19940107			
	US 1995-370574	19950106			
	US 1995-429206	19950426			
	WO 1996-US5500	19960417			

AB Pharmaceutical **formulations** contg. a lipophilic compd. solubilized in ethanol and a surfactant are disclosed. The solubilized compd. can then be further dissolved in a pharmaceutically acceptable aq. soln. to form a pharmaceutical **formulation** suitable for patient administration. Preferred lipophilic compds. are 5-methylisoxazole-4-carboxylic acid-(4-trifluoromethyl)-anilide and N-(4-triflouromethylphenyl)-2-cyano-3-hydroxycrotonamide. The soly. of leflunomide in a soln. of 66% Polysorbate 80 and 33% ethanol was 50 mg/mL.

IT **75706-12-6**, Leflunomide **108605-62-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical **formulations** for lipophilic compds. comprising ethanol and surfactant)

L45 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:25531 HCAPLUS
DN 126:84259
TI Single- and multiple-dose pharmacokinetics and pharmacodynamics of leflunomide's active metabolite A77 1726 in normal Lewis rats
AU Silva, H. T.; Shorthouse, R.; Morris, R. E.
CS School Medicine, Stanford University, Stanford, CA, 94305-5247, USA
SO Transplant. Proc. (1996), 28(6), 3092-3094
CODEN: TRPPA8; ISSN: 0041-1345
PB Appleton & Lange
DT Journal
LA English
AB In rats, 24 h after the administration of a single dose of 5 or 10 mg/kg of leflunomide, A77 1726 blood concns. were 5.2 and 8.3 mg/L, which resulted in 92.4 and 84.3% inhibition of [3H]thymidine incorporation (measure of lymphocyte proliferation), resp. On the other hand, in the studies performed after the administration of 14 doses of leflunomide, trough A77 1726 blood concns. (C24) were 0.7 and 1.0 mg/L, causing 39.0%

(5 mg/kg) and 20.0% inhibition of [3H]thymidine incorporation. The changes obsd. in kinetic parameters after the administration of multiple doses of leflunomide in the same way A77 1726 blood concns. and its effect on [3H]thymidine incorporation, clearly demonstrating the correlation between A77 1726 pharmacokinetics and pharmacodynamics. Further studies are required to detn. whether the **combined** pharmacokinetic and pharmacodynamic profiles are correlated with inhibition of the immune system.

IT **108605-62-5**, A771726
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(single- and multiple-dose pharmacokinetics and pharmacodynamics of leflunomide's active metabolite A77 1726 in normal Lewis rats in relation to lymphocyte proliferation inhibition and immunosuppression)

IT **75706-12-6**, Leflunomide
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(single- and multiple-dose pharmacokinetics and pharmacodynamics of leflunomide's active metabolite A77 1726 in normal Lewis rats in relation to lymphocyte proliferation inhibition and immunosuppression)

L45 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:756627 HCAPLUS
DN 126:22905
TI Injectable **formulations** for lipophilic compounds
IN Schwartz, Donna Pruess; Shawver, Laura Kay
PA Sugen, Inc., USA; Schwartz, Donna Pruess; Shawver, Laura Kay
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9633745	A1	19961031	WO 1996-US5500	19960417
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5610173	A	19970311	US 1995-429206	19950426
	AU 9655604	A1	19961118	AU 1996-55604	19960417
	AU 700423	B2	19990107		
	EP 830145	A1	19980325	EP 1996-912954	19960417
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 10511683	T2	19981110	JP 1996-532614	19960417
	NO 9704868	A	19971022	NO 1997-4868	19971022
PRAI	US 1995-429206	19950426			
	US 1994-179570	19940107			
	US 1995-370574	19950106			
	WO 1996-US5500	19960417			

AB The present invention features pharmaceutical **formulations** contg. a lipophilic compd., such as 5-methylisoxazole-4-carboxylic acid-(4-trifluoromethyl)-anilide (I) and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide. The lipophilic compd. is solubilized in a

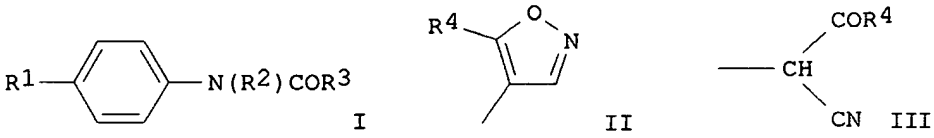
soln. contg. alc. (i.e. ethanol) and a surfactant. The solubilized compd. can be further dissolved in a pharmaceutically acceptable aq. soln., to form a **formulation** suitable for administration. The **formulation** is preferably used for parenteral administration. I was dissolved in a mixt. contg. Polysorbate 80 66 and ethanol 33 %, to a concn. of 50 mg/mL and its max. diln. rate with 0.9 % NaCl soln. was .gtoreq.1:100.

IT **75706-12-6**, Leflunomide **108605-62-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable **formulations** for lipophilic compds. for treatment of hyperproliferative cell disorder)

L45 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:425315 HCAPLUS
DN 125:67757
TI Preventive and remedy for type I allergic diseases
IN Amano, Yukio; Mizushima, Yuko; Ogata, Kenji
PA Hoechst Japan Limited, Japan
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9611682	A1	19960425	WO 1995-JP2027	19951004
	W: AU, CA, FI, HU, JP, KR, MX, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, NL, PT, SE				
	CA 2202904	AA	19960425	CA 1995-2202904	19951004
	AU 9536186	A1	19960506	AU 1995-36186	19951004
	AU 695907	B2	19980827		
	EP 787491	A1	19970806	EP 1995-933609	19951004
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	HU 77135	A2	19980302	HU 1997-1910	19951004
	ZA 9508708	A	19960514	ZA 1995-8708	19951016
	FI 9701584	A	19970415	FI 1997-1584	19970415
	NO 9701743	A	19970416	NO 1997-1743	19970416
	US 5814649	A	19980929	US 1997-817241	19970606
PRAI	JP 1994-250293	19941017			
	WO 1995-JP2027	19951004			

OS MARPAT 125:67757
GI



AB A **compn.** for preventing or treating type I allergic diseases comprises as the active ingredient an anilide compd. represented by general **formula** (I), a stereoisomer thereof, or a physiol. acceptable salt thereof, wherein R1 represents trifluoromethyl, halogeno or cyano; R2 represents hydrogen or linear or branched C1-C4 alkyl; and R3represents a group represented by general **formula** (II) or (III), wherein R4 represents linear or branched C1-C4 alkyl, linear or

branched C2-C6 alkenyl, linear or branched C2-C6 alkynyl, or C3-C7 cycloalkyl. The **compn.** can radically prevent or treat type I allergic diseases by inhibiting the prodn. of IgE as a direct cause of these diseases.

IT **75706-12-6 108605-62-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventive and remedy for type I allergic diseases)

L45 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:188953 HCAPLUS
DN 124:220512
TI Use of leflunomide to control and reverse chronic allograft rejection and to prevent or control xenograft rejection
IN Williams, James W.
PA USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9601111	A1	19960118	WO 1995-US8246	19950630
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5624946	A	19970429	US 1994-270908	19940705
	AU 9529541	A1	19960125	AU 1995-29541	19950630
	US 5688824	A	19971118	US 1996-598149	19960207
PRAI	US 1994-270908	19940705			
	WO 1995-US8246	19950630			

AB Methods are disclosed for controlling or reversing chronic rejection of allografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of cyclosporine A, FK506, rapamycin and corticosteroids. Also disclosed are methods of preventing or controlling acute and chronic rejection of xenografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of cyclosporine A, FK506, rapamycin and corticosteroids. The effect of e.g. leflunomide alone or with cyclosporine A on chronic rejection of rat cardiac allografts and on rejection od concordant hamster to rat cardiac xenografts is described.

IT **75706-12-6**, Leflunomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leflunomide or A771726, alone or in immunosuppressant **combination**, to control and reverse chronic allograft rejection and to prevent or control xenograft rejection)

IT **108605-62-5**, A771726
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leflunomide or A771726, alone or in immunosuppressant **combination**, to control and reverse chronic allograft rejection and to prevent or control xenograft rejection)

L45 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1995:580830 HCAPLUS
DN 122:322518
TI Pharmaceutical **composition** for parenteral, enteral and dermal administration of essentially insoluble drugs
IN Reul, Bernhard; Petri, Walter; Winkler, Irvin
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 649660	A2	19950426	EP 1994-116552	19941020
	EP 649660	A3	19960731		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	DE 4336434	A1	19950427	DE 1993-4336434	19931026
	CA 2134293	AA	19950427	CA 1994-2134293	19941025
	JP 07187995	A2	19950725	JP 1994-259928	19941025
PRAI	DE 1993-4336434		19931026		

AB The title **compn.** contains a drug which is essentially insol. in water and lipophilic media and .gtoreq.1 physiol. acceptable amphosurfactant which is sol. or forms micellar-colloidal solns. in water, dissolved in an anhyd. water-miscible solvent. This soln. is mixed with water to form a metastable micellar-colloidal dispersion suitable for enteral or parenteral administration. Thus, a dispersion conc. contg. 95.7% HBY 793 5.73, epicholine 75 69.50, and glycofurol 75 480.77 was mixed with water 5000.00 mg to form a soln.
IT **75706-12-6**, Leflunomide **108605-62-5**, 2-Cyano-3-hydroxy-N-(4-trifluoromethylphenyl)crotonamide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical **compn.** for parenteral, enteral and dermal administration of essentially insol. drugs)

L45 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1994:672170 HCAPLUS
DN 121:272170
TI Fluoroisoxazolecarboxamide and fluorocrotonamide derivatives for treatment of skin disorders
IN Kurtz, Ellen Smith; Weithmann, Klaus Ulrich; Bartlett, Robert Ryder
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

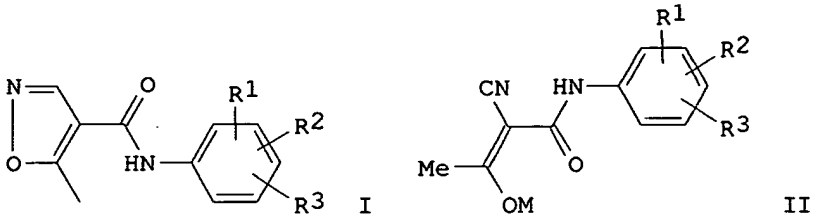
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 617959	A1	19941005	EP 1994-104678	19940324
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AU 9459157	A1	19941006	AU 1994-59157	19940329
	AU 670491	B2	19960718		
	IL 109151	A1	19981227	IL 1994-109151	19940329
	CA 2120319	AA	19941001	CA 1994-2120319	19940330
	ZA 9402257	A	19941116	ZA 1994-2257	19940330
	JP 06329538	A2	19941129	JP 1994-60374	19940330
	HU 70757	A2	19951030	HU 1994-908	19940330

HU 216194 B 19990528
PRAI US 1993-41223 19930331
OS MARPAT 121:272170
AB The title **compns**. are useful for treatment of skin disorders. Thus, a soln. of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide was heated with a soln. of NaOH, followed by acidification with HCl to obtain N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (I). The IC50 of I against cultured human epidermal keratinocyte was 15.5 .mu.M.
IT **75706-12-6P 108605-62-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(fluoroisoxazolecarboxamide and fluorocrotonamide derivs. for treatment of skin disorders)

L45 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 1999 ACS
AN 1991:415631 HCAPLUS
DN 115:15631
TI Pharmaceutical **compositions** containing 5-methyl-isoxazole-4-carboxylic acid anilides and 2-hydroxyethylidene cyanoacetic acid anilides for the treatment of ocular diseases with immune ethiology
IN Robertson, Stella M.; Lang, Laura Smith
PA Alcon Laboratories, Inc., USA
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

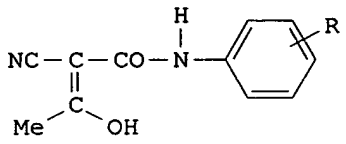
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 413329	A2	19910220	EP 1990-115691	19900816
	EP 413329	A3	19920415		
	EP 413329	B1	19970205		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	DD 297328	A5	19920109	DD 1990-343461	19900815
	JP 03090024	A2	19910416	JP 1990-215129	19900816
	AT 148628	E	19970215	AT 1990-115691	19900816
	ES 2099700	T3	19970601	ES 1990-115691	19900816
	CA 2023560	AA	19910219	CA 1990-2023560	19900817
	AU 9061104	A1	19910221	AU 1990-61104	19900817
	AU 633346	B2	19930128		
	ZA 9006544	A	19910626	ZA 1990-6544	19900817
	HU 59600	A2	19920629	HU 1990-5064	19900817
	HU 215959	B	19990329		
	IL 95412	A1	19960131	IL 1990-95412	19900817
	US 5583150	A	19961210	US 1994-317276	19941004
	US 5677335	A	19971014	US 1996-674368	19960702

PRAI US 1989-395860 19890818
US 1990-569671 19900817
US 1992-835243 19920212
US 1994-317276 19941004
OS MARPAT 115:15631
GI



I

II



III

AB The title **compns**. contain I [R1-R3 = (un)halo-substituted C1-3 alkyl, (un)halo-substituted C1-3 alkoxy, (un)halo-substituted C1-3 alkylthio, halo, nitro, cyano, etc.], a metabolite of I which is II [R1-R3 = halo, (un)halo-substituted C1-4 alkyl, (un)halo-substituted C1-3 alkoxy, (un)halo-substituted C1-3 alkylthio, etc.; M = H, alkali metal, ammonium], or III (R = 4-Cl, 3-Br, 4-NO2, etc.). Aq. suspension and ointment **formulations** contg. leflunomide are given.

IT **75706-12-6 108605-62-5**
RL: BIOL (Biological study)
(ophthalmic pharmaceutical of, for treatment of ocular disease with immune etiol.)

=> d his l47-

(FILE 'REGISTRY' ENTERED AT 11:33:59 ON 25 JUL 1999)

FILE 'REGISTRY' ENTERED AT 11:34:18 ON 25 JUL 1999

FILE 'HCAPLUS' ENTERED AT 11:35:07 ON 25 JUL 1999

FILE 'USPATFULL' ENTERED AT 11:35:30 ON 25 JUL 1999
L47 0 S L23
L48 15 S L14 AND L32
L49 15 S L48 AND (COMPOSITION OR COMBIN? OR FORMUL? OR SYNERG?)/BI,AB

=> fil uspat
FILE 'USPATFULL' ENTERED AT 11:36:35 ON 25 JUL 1999
CA INDEXING COPYRIGHT (C) 1999 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 13 Jul 1999 (19990713/PD)
FILE LAST UPDATED: 14 Jul 1999 (19990714/ED)
HIGHEST PATENT NUMBER: US5924128
CA INDEXING IS CURRENT THROUGH 14 Jul 1999 (19990714/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 13 Jul 1999 (19990713/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: May 1998
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 1998

>>> Page images are available for patents from 1/1/96. Current <<<
>>> week patent text is typically loaded by Thursday morning and <<<
>>> page images are available for display by the end of the day. <<<
>>> Image data for the /FA field are available the following week. <<<

>>> Complete CA file indexing for chemical patents (or equivalents) <<<
>>> is included in file records. A thesaurus is available for the <<<
>>> USPTO Manual of Classifications in the /NCL, /INCL, and /RPCL <<<
>>> fields. This thesaurus includes catchword terms from the <<<
>>> USPTO/MOC subject headings and subheadings. Thesauri are also <<<
>>> available for the WIPO International Patent Classification <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4, <<<
>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l49 bib abs hitrn tot

L49 ANSWER 1 OF 15 USPATFULL
AN 1998:119162 USPATFULL
TI Preventive and remedy for type 1 allergic diseases
IN Amano, Yukio, Hidaka, Japan
Mizushima, Yuko, Tokyo, Japan
Ogata, Kenji, Otawara, Japan
PA Hoechst Pharmaceuticals & Chemicals K.K., Tokyo, Japan (non-U.S. corporation)
PI US 5814649 19980929
WO 9611682 19960425
AI US 1997-817241 19970606 (8)
WO 1995-JP2027 19951004
19970606 PCT 371 date
19970606 PCT 102(e) date
PRAI JP 1994-250293 19941017
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 504
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical **composition** for prophylaxis or treatment of Type I allergic diseases which comprises as an active ingredient an anilide compound represented by the general **formula** (I) ##STR1## [wherein R.sub.1 is a trifluoromethyl group, a halogen atom or a cyano group, R.sub.2 is a hydrogen atom or a straight or branched C.sub.1 -C.sub.4 alkyl group and R.sub.3 is a group of the **formula** (II) or (III) ##STR2## (wherein R.sub.4 is a straight or branched C.sub.1 -C.sub.4 alkyl group, a straight or branched C.sub.2 -C.sub.6 alkenyl group, a straight or branched C.sub.2 -C.sub.6 alkynyl group or a C.sub.2 -C.sub.6 cycloalkyl group) or a stereoisomer thereof or a physiologically acceptable salt thereof.

The present **composition** remarkably inhibits the production of IgE, which is the direct cause of Type I allergic diseases, and it can radically prevent or cure Type I allergic diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5**
(preventive and remedy for type I allergic diseases)

L49 ANSWER 2 OF 15 USPATFULL
AN 1998:28101 USPATFULL
TI Pharmaceuticals for the treatment of rejection reactions in organ transplantations
IN Bartlett, Robert Ryder, Darmstadt, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5728721 19980317
AI US 1992-932577 19920820 (7)
PRAI DE 1991-4127737 19910822
DT Utility
EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Moezie, M.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 310
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use of compound 1 and/or 2 of the **formulae** ##STR1## and of physiologically tolerable salts of compound 2 for the treatment of rejection reactions of the organ recipient to the transplanted organ is described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6P 108605-62-5P**
(prepn. of, as immunosuppressant for organ transplant rejection treatment)

L49 ANSWER 3 OF 15 USPATFULL
AN 97:107110 USPATFULL
TI Use of leflunomide to prevent or control xenograft rejection
IN Williams, James, 655 Superior, Oak Park, IL, United States 60302
PI US 5688824 19971118
AI US 1996-598149 19960207 (8)
RLI Division of Ser. No. US 1994-270908, filed on 5 Jul 1994, now patented, Pat. No. US 5624946
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Marshall, O'Toole, Gerstein, Murray & Borun
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1369
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods of controlling or reversing chronic rejection of allografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of Cyclosporine A, FK506, rapamycin and corticosteroids. The invention also relates to methods of preventing or controlling acute and chronic rejection of xenografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of Cyclosporine A, FK506, rapamycin and corticosteroids.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6,** Leflunomide
(leflunomide or A771726, alone or in immunosuppressant combination, to

control and reverse chronic allograft rejection and to prevent or control xenograft rejection)
IT **108605-62-5**, A771726
(leflunomide or A771726, alone or in immunosuppressant combination, to control and reverse chronic allograft rejection and to prevent or control xenograft rejection)

L49 ANSWER 4 OF 15 USPATFULL
AN 97:96900 USPATFULL
TI Medicaments to combat autoimmune diseases
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Schleyerbach, Rudolf, Hofheim am Taunus, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5679709 19971021
AI US 1995-478847 19950607 (8)
RLI Division of Ser. No. US 1993-119840, filed on 13 Sep 1993, now patented, Pat. No. US 5459163 which is a division of Ser. No. US 1992-870327, filed on 17 Apr 1992, now patented, Pat. No. US 5268382 which is a continuation of Ser. No. US 1990-575603, filed on 31 Aug 1990, now abandoned which is a division of Ser. No. US 1986-911328, filed on 25 Sep 1986, now patented, Pat. No. US 4965276
PRAI DE 1985-3534440 19850927
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 384
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical **composition** for use in the treatment of chronic Graft-versus-host diseases as well as autoimmune diseases, in particular for the treatment of systemic lupus erythematosus containing as an active ingredient at least one compound of the **formula** 1 or 2 ##STR1## the latter being present per se or in the form of a physiologically tolerable salt.

The invention also relates to a dosage unit form of said pharmaceutical **composition** and a method of treating chronic Graft-versus host diseases as well as autoimmune diseases, in particular systemic lupus erythematosus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5 108605-62-5D**, salts
(graft-vs.-host and autoimmune diseases treatment with)

L49 ANSWER 5 OF 15 USPATFULL
AN 97:94267 USPATFULL
TI 5-methyl-isoxazole-4-carboxylic acid anilides and 2-hydroxyethylidene-cyano acetic acid anilides for the treatment of ocular disease
IN Robertson, Stella M., Arlington, TX, United States
Lang, Laura Smith, Bedford, TX, United States
PA Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)
PI US 5677335 19971014
AI US 1996-674368 19960702 (8)

RLI Division of Ser. No. US 1994-317276, filed on 4 Oct 1994, now patented, Pat. No. US 5583150 which is a continuation of Ser. No. US 1992-835243, filed on 12 Feb 1992, now abandoned which is a continuation of Ser. No. US 1990-569671, filed on 17 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-395860, filed on 18 Aug 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Fay, Zohreh
LREP Yeager, Sally
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 278
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use of 5-methyl-isoxazole-4-carboxylic acid anilides and 2-hydroxyethylidene-cyano acetic acid anilides for treating ocular diseases with immune etiology is disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5**
(ophthalmic pharmaceutical of, for treatment of ocular disease with immune etiol.)

L49 ANSWER 6 OF 15 USPATFULL
AN 97:36206 USPATFULL
TI Use of leflunomide to control and reverse chronic allograft rejection
IN Williams, James, 655 Superior, Oak Park, IL, United States 60302
PI US 5624946 19970429
AI US 1994-270908 19940705 (8)
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Marshall, O'Toole, Gerstein, Murray & Borun
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods of controlling or reversing chronic rejection of allografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of Cyclosporine A, FK506, rapamycin and corticosteroids. The invention also relates to methods of preventing or controlling acute and chronic rejection of xenografts in a transplantation patient by administering leflunomide product alone, or in **combination** with one or more immunosuppressive agents selected from the group consisting of Cyclosporine A, FK506, rapamycin and corticosteroids.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6**, Leflunomide
(leflunomide or A771726, alone or in immunosuppressant combination, to control and reverse chronic allograft rejection and to prevent or control xenograft rejection)
IT **108605-62-5**, A771726
(leflunomide or A771726, alone or in immunosuppressant combination, to control and reverse chronic allograft rejection and to prevent or control xenograft rejection)

L49 ANSWER 7 OF 15 USPATFULL

AN 97:20542 USPATFULL
TI **Formulations** for lipophilic compounds
IN Schwartz, Donna P., San Mateo, CA, United States
Shawver, Laura K., San Francisco, CA, United States
PA Sugen, Inc., Redwood City, CA, United States (U.S. corporation)
PI US 5610173 19970311
AI US 1995-429206 19950426 (8)
RLI Continuation-in-part of Ser. No. US 1995-370574, filed on 6 Jan 1995 which is a continuation-in-part of Ser. No. US 1994-179570, filed on 7 Jan 1994
DT Utility
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Lyon & Lyon
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 653
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pharmaceutical **formulations** containing a lipophilic compound solubilized in ethanol and a surfactant are disclosed. The solubilized compound can then be further dissolved in a pharmaceutically acceptable aqueous solution to form a pharmaceutical **formulation** suitable for patient administration. Preferred lipophilic compounds are 5-methylisoxazole-4-carboxylic acid-(4-trifluoromethyl)-auilide and N-(4-triflouromethylphenyl)-2-cyano-3-hydroxycrotonamide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6**, Leflunomide **108605-62-5**
(pharmaceutical formulations for lipophilic compds. comprising ethanol and surfactant)

L49 ANSWER 8 OF 15 USPATFULL
AN 96:113945 USPATFULL
TI 5-methyl-isoxazole-4-carboxylic acid anilides and 2-hydroxyethylidene-cyano acetic anilides for the treatment of ocular diseases
IN Robertson, Stella M., Arlington, TX, United States
Lang, Laura S., Bedford, TX, United States
PA Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)
PI US 5583150 19961210
AI US 1994-317276 19941004 (8)
RLI Continuation of Ser. No. US 1992-835243, filed on 12 Feb 1992, now abandoned which is a continuation of Ser. No. US 1990-569671, filed on 17 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-395860, filed on 18 Aug 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Fay, Zohreh
LREP Yeager, Sally
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 252
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use of 5-methyl-isoxazole-4-carboxylic acid anilides and 2-hydroxyethylidene-cyano acetic acid anilides for treating ocular diseases with immune etiology is disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5**

(ophthalmic pharmaceutical of, for treatment of ocular disease with immune etiol.)

L49 ANSWER 9 OF 15 USPATFULL
AN 96:58233 USPATFULL
TI Isoxazole-4-carboxamides and hydroxyalkylidenecyanoacetamides, pharmaceuticals containing these compounds and their use
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5532259 19960702
AI US 1995-476278 19950607 (8)
DCD 20121116
RLI Division of Ser. No. US 1992-938048, filed on 16 Nov 1992, now patented, Pat. No. US 5494911
PRAI DE 1990-4016178 19900518
DE 1990-4017020 19900526
DE 1990-4017043 19900526
DT Utility
EXNAM Primary Examiner: McKane, Joseph K.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1166
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Isoxazole-4-carboxamides and hydroxyalkylidenecyanoacetamides, pharmaceuticals containing these compounds and their use

Isoxazole-4-carboxamide derivatives and hydroxyalkylidene-cyanoacetamide derivatives are suitable for the treatment of carcinoses. These compounds can be prepared by known processes. Some of the compounds are novel and are additionally suitable for the treatment of rheumatic disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6P 108605-62-5P**
(prepn. of, as neoplasm inhibitor and antirheumatic)

L49 ANSWER 10 OF 15 USPATFULL
AN 96:43693 USPATFULL
TI Method of treating hyperproliferative vascular disease
IN Morris, Randall E., Stanford, CA, United States
Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5519042 19960521
AI US 1994-181116 19940113 (8)
DT Utility
EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Weddington, Kevin E.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of preventing or treating hyperproliferative vascular disease in a mammal consists of administering to a mammal an effective amount of carboxyamide compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6P 108605-62-5P**
(treatment of hyperproliferative vascular disease with fluorophenylisoxazolecarbooxamide and flurorophenycyanocrotonamide derivs.)

L49 ANSWER 11 OF 15 USPATFULL
AN 96:27194 USPATFULL
TI Pharmaceutical for the treatment of skin disorders
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Weithmann, Klaus U., Hofheim, Germany, Federal Republic of
Kurtz, Ellen S., Flemington, NJ, United States
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
Hoechst-Roussel Pharmaceuticals, Inc., North Somerville, NJ, United States (U.S. corporation)
PI US 5504084 19960402
AI US 1994-216332 19940323 (8)
RLI Continuation-in-part of Ser. No. US 1993-41223, filed on 31 Mar 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Weddington, K.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pharmaceutical for the treatment of skin disorders

A compound of the **formula** I or II ##STR1## and physiologically tolerable salts of compound of the **formula** II are suitable for treatment of psoriasis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6P**
(tifluorophenylmethylisoxazolecarboxamides or cyanohydroxycrotonamide pharmaceuticals for treatment of skin disorders in humans)
IT **108605-62-5P**
(tifluorophenylmethylisoxazolecarboxamides or cyanohydroxycrotonamide pharmaceuticals for treatment of skin disorders in humans)

L49 ANSWER 12 OF 15 USPATFULL
AN 96:16988 USPATFULL
TI Isoxazole-4-carboxamides and hydroxyalkylidenecyanoacetamides, pharmaceuticals containing these compounds and their use
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5494911 19960227
WO 9117748 19911128
AI US 1992-938048 19921116 (7)

WO 1990-EP1800 19901024
19921116 PCT 371 date
19921116 PCT 102(e) date
PRAI DE 1990-4016178 19900518
DE 1990-4017020 19900526
DE 1990-4017043 19900526
DT Utility
EXNAM Primary Examiner: McKane, Joseph K.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1116
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Isoxazole-4-carboxamide derivatives and hydroxyalkylidene-cyanoacetamide derivatives are suitable for the treatment of carcinoses. These compounds can be prepared by known processes. Some of the compounds are novel and are additionally suitable for the treatment of rheumatic disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6P 108605-62-5P**
(prepn. of, as neoplasm inhibitor and antirheumatic)

L49 ANSWER 13 OF 15 USPATFULL
AN 95:92810 USPATFULL
TI Medicament to combat autoimmune diseases
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Schleyerbach, Rudolph, Hofheim am Taunus, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt, Germany, Federal Republic of (non-U.S. corporation)
PI US 5459163 19951017
AI US 1993-119840 19930913 (8)
RLI Division of Ser. No. US 1992-870327, filed on 17 Apr 1992, now patented, Pat. No. US 5268382 which is a continuation of Ser. No. US 1990-575603, filed on 31 Aug 1990, now abandoned which is a division of Ser. No. US 1986-911328, filed on 25 Sep 1986, now patented, Pat. No. US 4965276
PRAI DE 1985-3534440 19850927
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical **composition** for use in the treatment of chronic Graft-versus-host diseases as well as autoimmune diseases, in particular for the treatment of systemic lupus erythematosus containing as an active ingredient at least one compound of the **formulae** 1 or 2 ##STR1## the latter being present per se or in the form of a physiologically tolerable salt.

The invention also relates to a dosage unit form of said pharmaceutical **composition** and a method of treating chronic Graft-versus host diseases as well as autoimmune diseases, in particular systemic lupus erythematosus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5 108605-62-5D**, salts
(graft-vs.-host and autoimmune diseases treatment with)

L49 ANSWER 14 OF 15 USPATFULL
AN 93:102794 USPATFULL
TI Medicaments to combat autoimmune diseases, in particular systemic lupus erythematosus
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Schleyerbach, Rudolf, Hofheim am Taunus, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5268382 19931207
AI US 1992-870327 19920417 (7)
RLI Continuation of Ser. No. US 1990-575603, filed on 31 Aug 1990, now abandoned which is a division of Ser. No. US 1986-911328, filed on 25 Sep 1986, now patented, Pat. No. US 4965276
PRAI DE 1985-3534440 19850927
DT Utility
EXNAM Primary Examiner: Schenkman, Leonard
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical **composition** for use in the treatment of chronic Graft-versus-host diseases as well as autoimmune diseases, in particular for the treatment of systemic lupus erythematosus containing as an active ingredient at least one compound of the **formulae** 1 or 2 ##STR1## the latter being present per se or in the form of a physiologically tolerable salt.

The invention also relates to a dosage unit form of said pharmaceutical **composition** and a method of treating chronic Graft-versus-host diseases as well as autoimmune diseases, in particular systemic lupus erythematosus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5 108605-62-5D**, salts
(graft-vs.-host and autoimmune diseases treatment with)

L49 ANSWER 15 OF 15 USPATFULL
AN 90:81803 USPATFULL
TI Medicaments to combat chronic graft-versus-host diseases
IN Bartlett, Robert R., Darmstadt, Germany, Federal Republic of
Schleyerbach, Rudolf, Hofheim am Taunus, Germany, Federal Republic of
Kammerer, Friedrich-Johannes, Hochheim am Main, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt, Germany, Federal Republic of (non-U.S. corporation)
PI US 4965276 19901023
AI US 1986-911328 19860925 (6)
PRAI DE 1985-3534440 19850927
DT Utility
EXNAM Primary Examiner: Schenkman, Leonard

LREP Finnegan, Henderson, Farabow, Garrett, and Dunner
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 363
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical **composition** for use in the treatment of chronic Graft-versus-host diseases as well as autoimmune diseases, in particular for the treatment of systemic lupus erythematosus containing as an active ingredient at least one compound of the **formulae** 1 or 2 ##STR1## the latter being present per se or in the form of a physiologically tolerable salt.

The invention also relates to a dosage unit form of said pharmaceutical **composition** and a method of treating chronic Graft-versus host diseases as well as autoimmune diseases, in particular systemic lupus erythematosus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **75706-12-6 108605-62-5 108605-62-5D**, salts
(graft-vs.-host and autoimmune diseases treatment with)

=> d his 150-

(FILE 'USPATFULL' ENTERED AT 11:36:35 ON 25 JUL 1999)

FILE 'REGISTRY' ENTERED AT 11:36:49 ON 25 JUL 1999

FILE 'USPATFULL' ENTERED AT 11:36:57 ON 25 JUL 1999
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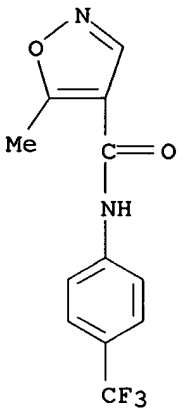
L50 SEL L49 1- RN : 162 TERMS
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:36:59 ON 25 JUL 1999
L51 162 S L50
L52 1 S L51 AND L14
L53 1 S L51 AND L32

=> d ide can 152

L52 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1999 ACS
RN **75706-12-6** REGISTRY
CN 4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN HWA 486
CN Leflunomide
CN SU 101
CN SU 101 (pharmaceutical)
FS 3D CONCORD
DR 210165-51-8
MF **C12 H9 F3 N2 O2**
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



229 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
229 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:29577

REFERENCE 2: 131:27618

REFERENCE 3: 131:27612

REFERENCE 4: 131:27611

REFERENCE 5: 131:13589

REFERENCE 6: 131:387

REFERENCE 7: 130:352088

REFERENCE 8: 130:346723

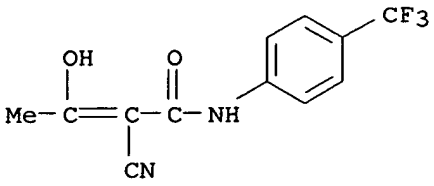
REFERENCE 9: 130:306209

REFERENCE 10: 130:280811

=> d ide can l53

L53 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1999 ACS
RN **108605-62-5** REGISTRY
CN 2-Butenamide, 2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Cyano-3-hydroxy-N-(4-trifluoromethylphenyl)crotonamide
CN A 77-1726
CN SU 20
CN Teriflunomide
FS 3D CONCORD
DR 210165-52-9
MF **C12 H9 F3 N2 O2**

CI COM
SR CA
LC STN Files: BIOSIS, CA, CANCERLIT, CAPLUS, EMBASE, MEDLINE, TOXLIT, USPATFULL



79 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
79 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:39350

REFERENCE 2: 131:29577

REFERENCE 3: 131:27612

REFERENCE 4: 131:27611

REFERENCE 5: 131:27610

REFERENCE 6: 131:27609

REFERENCE 7: 131:27608

REFERENCE 8: 131:13589

REFERENCE 9: 130:280811

REFERENCE 10: 130:246540